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The overall goal of these studies is to characterize the effects of noradrenergic (NA) afferents on cortical information processing. Our previous studies indicate that the primate locus coeruleus (LC) system, originating in the pontine brainstem, innervates neocortex more densely than previously thought, exhibiting highly specific patterns in terms of the regional and laminar distribution of its axons across the neocortex. Previous neurophysiological observations suggest that this highly divergent system imposes state-related modulatory effects on thalamo-cortical and cortico-cortical systems. For example, we have shown that primate LC-NA neurons are more active during waking than sleep and exhibit bursts of activity during increases in attentiveness. We have also previously demonstrated that the microiontophoretic application of NA to monkey auditory cortex neurons increases the selectiveness of their responses to auditory stimuli.

In studies conducted during Years 01-03, we have demonstrated that LC lesions in monkeys interfere with the production of a surface-positive wave that mimics many of the

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characteristics of the human P300 event-related potential (ERP). We have also found that LC activation, induced by microinfusion of drugs into the LC, produces electroencephalographic (EEG) signs of arousal in both neocortex and hippocampus. Specifically, the cortical EEG exhibits high frequency, low amplitude activity while the hippocampal EEG is dominated by theta rhythm. In addition, we have developed further assays for potential LC effects on forebrain function and we have refined our techniques for manipulating LC electrophysiological activity.

The studies we have proposed for Years 04-06 have the following Specific Aims: 1) To examine, in monkeys, the effects of manipulating the LC-NA system on ERPs, EEG characteristics, and associated behaviors in operant paradigms that utilize visual or auditory cues; 2) To correlate the activities of individual monkey LC-NA neurons with cortical neuronal activity and the same measures utilized in Aim 1; 3) To reproduce and extend our preliminary observation that activation of the LC by local drug infusion, in halothane-anesthetized rats, produces EEG signs of cortical and hippocampal activation; 4) To examine the relationship between the intensity of LC neuronal activity and rates of norepinephrine release in neocortex and hippocampus by performing microdialysis in these forebrain terminal regions in anesthetized rats during manipulation of LC activity.

These convergent experiments are necessary to rigorously determine whether LC-NA activity is necessary and/or sufficient for the full expression of particular aspects of cortical information processing.

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Organization of Technical Report. This report is organized into three sections that correspond to the Specific Aims for Years 01-03. In those instances where experimental exigencies and unexpected findings have led to the performance of experiments that were not anticipated in the original application, the logic for these developments has been described in order to make clear the relevance of the data generated to the Year 01-03 Specific Aims and to introduce the rationale for the Year 04-06 Specific Aims. The full-length, published reports describing studies completed during Years 01-03 are listed at the end of this report. The numbers in square brackets in this section refer to the corresponding publication from this list.

A. SPECIFIC AIM 1 (YEARS 01-03): TO CORRELATE THE ACTIVITY OF LC SOURCE NEURONS WITH SPECIFIC ELECTROPHYSIOLOGICAL OR BEHAVIORAL MEASURES OF AUDITORY INFORMATION PROCESSING IN PRIMATES

The investigation of LC-NA involvement in inducing state-related changes in cortical activity is predicated on the ability to assay cortical information processing using electrophysiological techniques and modeling such assays in animals in order to conduct invasive experimental tests of the hypothesis. Work with human subjects has shown that scalp-recorded EEG is a reliable measure of behavioral state, such as attentiveness or arousal, while event-related potentials (ERPs) are reliable indices of specific information processing functions. In order to utilize intra- and extracranially recorded EEG and ERP measures to assay the role of LC-NA in brain information processing, animal models of human ERPs were developed during Years 01-03. Considerable effort was invested in characterizing these assays in detail in monkeys and in demonstrating that features previously observed in human subjects are also present in monkeys. During Years 02-03, LC-NA activity was manipulated via electrolytic lesions or pharmacological agents in order to examine its relationship to the electrophysiological measures (see Specific Aim 2).

Auditory P300s. The human P300 has been one of the most extensively studied ERP components, and its antecedent conditions are well known. The most common type of P300 occurs following task-relevant stimuli which require a response (Active Paradigms). Other studies have shown that improbable, deviant stimuli that are not task relevant and do not require a response (Passive Paradigms) elicit P300 potentials (P3as) differing in scalp distribution. P3as and P3bs exhibit certain common properties and are thought to be manifestations of information processing functions that are activated by multimodal stimuli, are sensitive to the novelty and/or meaningfulness of the event, reflect perceptual rather than motor functions, and are sensitive to the allocation of task

resources. A number of psychological constructs, including context-updating, memory consolidation, orienting, resolution of uncertainty, and stimulus categorization, have been used to explain the variance associated with these events. Thus, P300 is an appropriate ERP measures for studying changes to information processing systems caused by a variety of manipulations including those affecting a particular brain monoaminergic system.

The studies we have completed to date suggest that monkey auditory and visual P300s in passive and in active operant conditions exhibit morphological and functional characteristics similar to those observed in human subjects [2,5]. That is, these are large positive potentials that: a) occur in response to infrequent or novel events embedded in a series of repetitive stimuli; b) begin approximately 150-200 msec after stimulus onset; c) have durations of hundreds of milliseconds; d) peak between 200-400 msec; e) are sensitive to the meaningfulness or relevance of the event; f) reflect the allocation of attentional resources, and g) have corresponding intracranial sources in the hippocampus and cingulate cortex.

Passive Paradigms. In the passive experiments [2], ERPs were recorded epidurally in untrained monkeys (Saimiri sciureus) exposed to sequences of auditory stimuli (2 kHz and 6 kHz tones, 40 msec duration, 60 dB above nHL, once a second). The paradigms consisted of presenting one tone 90% of the time, with randomly interspersed "oddball" events (i.e., the second tone) occurring 10% of the time. Stimulus probability and intertimulus interval were systematically varied in different sessions. P300-like responses were recorded following the "oddball" tones and were characterized by long latencies (200-300 msec), long-durations (200 msec), multiple peaks, and maximal amplitude over lateral parietal areas. Monkey P300 was also sensitive to the probability of the eliciting event, to the temporal sequence of stimuli, and to ISI. These properties resemble those previously reported for squirrel monkey P300 and those commonly reported for human P300. Indeed, our data suggest strong analogies between the two species.

Active Paradigms. Analogous experiments were performed in monkeys trained to respond, in a delayed fashion (i.e., 400 msec after stimulus onset), to the "oddball" events in order to receive a reward [5]. ERPs were recorded in response to the same stimuli used in the passive conditions. Different target tone probabilities were used in different sessions (i.e., .1, .3, .5). ERPs following targets typically included P300-like large, positive potentials with long peak latencies (250-400 msec), long duration (300 msec), and a broad scalp distribution having maximal amplitude over lateral parietal areas. Increased stimulus probability for the entire stimulus sequence (global probability) resulted in decreased P300 amplitudes, and differences in the stimulus sequences immediately preceding targets (local probability) also resulted in changes in P300 magnitude. Furthermore, larger amplitude monkey P300s were elicited when subjects were more fully engaged in the task, as indexed by their operant response level [5].

Visual P300s. One property of human P300 is its modality non-specificity. That is, P300s generally display similar properties whether elicited by auditory, visual, or somatosensory stimuli. One explanation for these similarities is that stimulation from different sensory modalities is channeled to common pathways to engages similar neural mechanisms. The studies just described have shown that an electrophysiological measure resembling the human P300 potential can be recorded in monkey using an appropriate auditory "oddball" paradigm [2,5]. In order to investigate the hypothesis that P300-like potentials occur in monkey in response to appropriate visual stimuli, we recorded visual ERPs (VEPs) from chronically implanted electrodes in seven squirrel monkeys (Saimiri sciureus). The results indicate that P300-like potentials can be recorded in a visual

"oddball" paradigm. These potentials exhibit sensitivity to stimulus probability and to trial-to-trial changes in stimulus sequence, two properties which characterize the human P300. These observations are significant because they demonstrate that another defining characteristic of the human P300 is also evident in monkey. A manuscript describing these results is currently in preparation. LC lesion studies, which will address what role LC-NA plays in the genesis of visual P300, are currently underway.

Intracranial P300s. The strategy of recording ERPs intracranially is useful in addressing the question of whether P300 is generated by a single cortical source or by a combination of cortical and subcortical sources. Observations in human have suggested that areas such as the hippocampus and frontal cortex may contribute to scalp-recorded activity. Recording intracranial ERPs will also be helpful in determining the extent of NA involvement at these various sites. We have chronically implanted two monkeys with twisted wire electrodes oriented towards the hippocampus (dentate gyrus) and specific cortical regions (e.g., cingulate, frontal, and parietal cortex). Subsequent histology on these subjects revealed that hippocampal electrodes were located anterior and medial to the target area, in entorhinal cortex. Nevertheless, large P300-like components, similar to those recorded at the scalp surface, were recorded from these sites. We are continuing to perform depth recordings in both auditory and visual paradigms.

Brainstem Auditory Evoked Potentials (BAEPS). Field potentials recorded on the scalp following the rapid presentation of short-duration acoustic stimuli reflect electrical activity in auditory nuclei and pathways in the brain stem. Initial observations reported in the literature suggested that each BAEP peak reflects the processing of acoustic signals in a specific brain stem site such as the VIIIth nerve, cochlear nucleus, superior olivary complex, lateral lemniscus, inferior colliculus, and medial geniculate and in the thalamocortical radiation, respectively. More recent observations argue that BAEP peaks reflect superposition of field potentials from multiple brain stem sources. Despite these interpretive difficulties, monkey BAEPs provide a sensitive assay of subcortical auditory function that can be utilized in studies involving manipulation of the LC-NA system. We have recorded BAEPs from chronically implanted epidural electrodes in ten squirrel monkeys (Saimiri sciureus). The effects of stimulus intensity, repetition rate, and anesthesia (Ketamine 20 mg/kg IM) on peak latencies and inter-peak intervals were evaluated [8]. As with human, monkey waveforms typically consisted of seven peaks (I-VII) which exhibited significant decreases in latency with increasing intensity (I-IV) and increases in latency with increases in repetition rate (III, V, and VI). Inter-peak intervals were also similar to those observed in human. Furthermore, ketamine anesthesia significantly delayed the latencies of most peaks, except I, V, and VII. These similarities between monkey and human suggest similarities in acoustic processing in the two species. Also, we have now established a standard protocol and normative data for these potentials. Since previous studies have suggested that central transmission along auditory pathways may in part be modulated by extrathalamic afferents to cortex. BAEPs provide us with an additional sensitive assay of activity to determine the site(s) of action of noradrenergic effects, i.e., whether cortical or pre-cortical. Preliminary studies suggest that extensive LC lesions affect BAEP peak latencies but not amplitudes.

Relationships of Stimulus Intensity to ERP Amplitude in Monkey. We have investigated the amplitude changes that occur in some ERP components with increasing stimulus intensity. In humans, the amplitudes of these components can either increase or decrease in response to increasing stimulus intensity

depending on the location of the surface recording site. Large increases characterize components presumably generated by modality-specific sites, while smaller increases, or even decreases, are evident in those originating in associational areas. Comparable data from non-human primates, which would permit invasive studies of the neural substrates underlying these amplitude differences are limited. To more fully characterize intensity-amplitude relationships, auditory ERPs were recorded from chronically implanted epidural electrodes in five squirrel monkeys in response to tones (500 Hz, 300 msec duration) of varying intensities (50, 60, 70, 80 dB SPL). Typically, peak ERP amplitudes recorded at mid-cortical sites (i.e., Fz, Cz, Pz) during the 200 msec interval following stimulus presentation increased substantially with increasing stimulus intensity. In contrast, only small increases or even decreases in amplitude were evident over lateral temporal sites (i.e., T3, T4). These site-specific response profiles exhibited considerable temporal stability. These data suggest that human and monkey exhibit similar responses to changes in stimulus intensity and provide a model to investigate the role of LC-NA in these intensity-amplitude phenomena (a report describing these results is in preparation).

EEG Characteristics as Predictors of ERP Amplitude. Previous reports have suggested that there is a strong relationship between ongoing EEG activity and the occurrence and amplitude of particular ERP components. In our monkey studies, P300 amplitude variance within individuals tends to be quite large from one session to the next. To study the role that behavioral state plays in producing such differences, we analyzed the relationship between EEG spectral frequencies and the amplitude and latency of various ERP components. Preliminary data indicate that enhancement of P300 and not earlier components occurs if the EEG is desynchronized at the time of stimulus presentation. Changes in the spectral density function of the EEG can be observed in analyses we have now implemented in the laboratory.

Operant training. We are now beginning to use cynomolgus monkeys (Macaca fascicularis) for our studies because they are capable of learning more complex operant tasks than the squirrel monkeys we have previously used. We have implemented methods for chairing and training this species, and 4 animals are now chair adapted and are being trained on an auditory "oddball" task. The P. I. has successfully performed stereotaxic surgery on this species of animal previously for anatomical studies, and the proposed surgeries are entirely feasible.

B. SPECIFIC AIM 2 (YEARS 01-03): CHARACTERIZE THE EFFECTS OF ACTIVATING OR SUPPRESSING THE SOURCE NEURONS OF NEOCORTICAL NORADRENERGIC INNERVATION ON ELECTROPHYSIOLOGICAL AND/OR BEHAVIORAL MEASURES OF AUDITORY INFORMATION PROCESSING IN PRIMATES

During Years 01-03 of this grant, 3 types of studies have been completed using local infusion of drugs into the LC in anesthetized rats: a) determination of the effects of drugs delivered in this fashion on LC neuronal activity, b) assessing the effects of LC activation on individual neurons in somatosensory cortex, and c) examination of the effects of LC activation or blockade on cortical and hippocampal EEG activity.

Effects of locally infused drugs on LC neuronal activity. Electrophysiological activity of individual locus coeruleus (LC) neurons was recorded in halothane-anesthetized rats before, during, and after the infusion of adrenergic, cholinergic, or peptidergic compounds about 400 um lateral to LC [6]. This was accomplished using a recording/infusion probe consisting of a stainless steel microelectrode cemented to a parallel guide tube for a 33 ga infusion needle. Infusion of the alpha-adrenergic agonist clonidine (CLON), in concentrations

ranging from 5-20 uM (67-270pg/50 nl injection), reversibly suppressed LC activity with latencies to onset of 5-15 min and durations of 20-120 min. During the onset of suppressed firing, responses to sensory stimuli (footshock) were relatively preserved, but at later times the reliablility of footshock responses was greatly reduced. The alpha-adrenergic antagonist piperoxane (PIP) rapidly reversed the inhibitory effects of CLON. Infusion of 0.1 ul of 0.02 M acetylcholine (ACh) produced a 3-4 min period of increased LC firing, with a 1 min latency to onset. Larger volumes (0.15 ul) produced greater increases in firing rate lasting 10-12 min. ACh effects were readily reversed with equimolar doses of scopolamine (SCOP). The effects of 0.02 M ACh were also rapidly reversed by equal volumes of 0.001 M CLON. SCOP and CLON reduced basal firing rates without blocking responses to sensory stimuli. Infusion of the cholinergic agonist carbamyl-beta-choline (carbachol) produced robust, reliable activation of LC neurons at doses of 25-1,000 ng per 100 nl injection. The electrophysiological effects of 3 adrenocorticotropin hormone (ACTH) fragments [1-24], [4-10], and [1-10] were also evaluated. ACTH[1-10] and ACTH[4-10] decreased LC activity for up to 2 hr. ACTH [1-24] exhibited more complex effects, with an increase in discharge rate being accompanied by a decrease in action potential amplitude. The results obtained with adrenergic and cholinergic agents are compatible with previous observations based on systemic or iontophoretic administration of these substances. The effects of ACTH infusion are more complex, with local infusion of these substances producing electrophysiological effects different from those obtained with iontophoretic techniques. The robust, reliable effects of local infusion of cholinergic or adrenergic agents on LC activity which were obtained using the parameters described in this report imply that such injections produce a simultaneous, reversible, verifiable increase or decrease in the mean discharge rate of a majority of LC neurons. In the proposed studies, as in the studies described immediately below, this method will be used to implement new strategies for examining the postsynaptic and behavioral effects of enhanced or diminished LC activity.

Effects of LC activation on neuronal activity in somatosensory cortex. The recording/infusion probe described above was used to activate the neurons of the LC in a reversible and verifiable manner in halothane-anesthetized rats. Infusions of bethanechol increased LC discharge rates 3- to 4-fold for a period of 3-5 min. Simultaneously, recordings were obtained from neurons in the hindlimb region of primary somatosensory cortex. These were activated by appropriate peripheral somatosensory stimuli (air puff or electrical stimulation delivered to the receptive field). Somatosensory responses and background activity were recorded during baseline conditions, LC activation, and LC recovery. Typically, several repetitions of this procedure were conducted for each cortical recording site, and only one recording site was tested per animal. The effects of LC stimulation were highly replicable both within and between animals. Baseline somatosensory responses consisted of a brief, short-latency activation followed by a longer duration pause, in which activity decreased to below background levels, and a gradual return to prestimulus discharge rates. During LC activation, the brief initial response was somewhat reduced, but the previous long-latency reduction in activity became an extended activation. Overall, the absolute magnitude of the total response was increased. Since background activity was reduced during LC activation, the ratio of stimulus-elicited to background activity was considerably enhanced. Thus, the effect of LC stimulation was similar in many regards to that previously reported for iontophoretic application of NE to cortical sensory neurons, although certain differences were also evident. A manuscript describing these results is in preparation and is included as item 10 of the Appendix.

Effects of LC activation on forebrain electroencephalographic (EEG) activity. In halothane-anesthetized rats, cortical EEG (ECoG) and hippocampal EEG (HEEG)

typically exhibit activity similar to that of a lightly sleeping animal. However, periods of "waking" EEG are sometimes observed spontaneously and are always observed following a stimulus such as a tail-pinch, even though the animal is still at a surgical level of anesthesia and does not overtly respond to any such stimulation (all of these phenomena are also observed in humans). We have also utilized the recording/infusion probe to activate the neurons of the LC in halothane-anesthetized rats while simultaneously recording EEG activity in frontal cortex and hippocampus. This experiment has now been performed in 15 animals, with the following findings: 1) LC activation is consistently followed, within 2 to 30 seconds, by ECoG desynchronization and hippocampal theta, 2) if the recording/infusion probe is located so that the infusion is not effective in activating LC neurons (e. g., is placed 1 mm dorsal or ventral to the LC), no such forebrain effects are produced by the infusion, 3) following infusion-induced activation, forebrain EEG returns to pre-infusion patterns with about the same time course as the recovery of LC activity (10-20 minutes for complete recovery), 4) whether infusions are made from sites medial or lateral to LC, forebrain EEG changes invariably follow LC activation with similar latencies. Thus, these data all point to LC activation as a crucial mediating event in producing the EEG effects that follow the carbachol infusions.

These observations are especially interesting because they provide evidence that LC activity levels are not only correlated with measures of forebrain activation but can be causally related to cortical and hippocampal EEG patterns. Specifically, LC activation may be sufficient, although possibly not necessary, for forebrain EEG activation.

In order to determine whether LC might be necessary as well as sufficient for forebrain EEG activation, we have now begun to also assess the effects of inactivating LC. As previously reported, LC neurons in these preparations respond with a brief burst of activity to a tail-pinch stimulus. Simultaneously, EEG signs of arousal occur, and these persist for up to several minutes. Thus, the sustained EEG activation does not appear to depend on LC activity in this situation. In 3 animals, we have also observed that blocking LC activation to tail-pinch, by locally infusing clonidine, does not block the forebrain activation induced by tail pinch. However, in 2 animals, we have made the complementary observation, i. e., systemic clonidine blocks the forebrain response to tail-pinch without blocking the LC response. LC activation is apparently sufficient, but not necessary, to induce EEG "activation." Also, there may be a direct forebrain or non-LC brainstem sedative effect of clonidine.

Effects of systemic drug administration on monkey P300. Pharmacologic activation or suppression of source-cell activity using systemically administered drugs provides another method of studying the relationship between LC activity and the variety of electrophysiological indices that measure cortical information processing. The role of NA-LC in the genesis of P300 was examined in the present study by recording event-related potentials (ERPs) in squirrel monkey (Saimiri sciureus) before and after systemic administrations of the alpha-2 adrenergic agonist, clonidine, in doses that are known to suppress the electrophysiological activity of LC neurons. Six chronically implanted monkeys, 2 trained and 4 untrained, were tested with 3 doses of clonidine (0.05, 0.075, 0.1 mg/kg IM) in an auditory "oddball" paradigm (1 and 6 KHz tones, 200 msec duration, one second ISI). Two of the untrained subjects showed habituation in P300-like potentials during the course of the study, thus their data were difficult to interpret. The remaining subjects showed significant decreases in P300 amplitude following clonidine administration, particularly at the highest dose, while showing recovery in post-drug sessions. These data suggest that NA-LC activity is specifically involved in the genesis of monkey P300 potentials elicited under passive (untrained) or active

(trained) conditions.

In a separate study, two trained and 4 untrained monkeys have been tested in the auditory "oddball" paradigm following systemic administration of the specific alpha-2 adrenergic agonist, guanfacine. Guanfacine is reported to be a more specific alpha-2 antagonist than clonidine and to not have its sedative effects. This study addresses the issue of whether the reductions in P300 amplitude described above were due to these sedative effects of clonidine. Preliminary results have been variable, with some subjects exhibiting an enhancement of P300-like activity, others showing a reduction, and still others showing no change. A finding that may bear on these conflicting results is currently being studied in greater detail by examining the relationship between behavioral state, as measured by the EEG, and the ERP. Preliminary data suggest that P300 is enhanced by guanfacine if the EEG is desynchronized and not affected if the EEG is synchronized.

C. SPECIFIC AIM 3 (YEARS 01-03): DETERMINE THE EFFECTS OF LESIONING NA SOURCE NEURONS OR THEIR CORTICAL EFFERENT PATHWAYS ON ELECTROPHYSIOLOGICAL AND/OR BEHAVIORAL MEASURES OF AUDITORY INFORMATION PROCESSING IN PRIMATES

Two types of studies relevant to this Specific Aim have been completed. First, we have continued our anatomical studies of the monoaminergic innervation of monkey neocortex since the ability to perform discrete, localized lesions of the NA innervation of neocortex depends upon methods for anatomically assaying the results of such lesions and upon basic descriptions of this innervation in normal animals. Second, we have studied the effects of LC lesions on auditory ERPs in monkeys.

Anatomical Studies. Over the past several years, we have utilized immunohistochemical methods to characterize the distributions of monoaminergic axons in several regions of monkey neocortex. The technical and anatomical knowledge developed in these studies has been used to evaluate the efficacy and specificity of the lesions described in the following section. In order to proceed with additional lesion studies which will involve circumscribed lesions of the NA innervation of particular cortical areas, even more sophisticated anatomical and technical knowledge is essential. To this end, we have continued our immunohistochemical studies of the monoaminergic innervation of monkey neocortex [1,3,4].

Effects of LC Lesions on Auditory ERPs. Small, bilateral, electrolytic lesions of the LC (1 mA, 15 secs) and knife cuts of the dorsal bundle (DB) fibers were made in five monkeys. ERPs were recorded in a passive "oddball" paradigm before and after lesions in order to assess whether they would produce an effect on monkey P300. LC and DB lesions were made by localizing the nucleus and creating an electrolytic lesion. Then, a knife cut was made at the anterior pole of the nucleus. Following these lesions, the magnitude of monkey P300 was significantly reduced in animals where damage to the LC nucleus was extensive, but not where the nucleus was relatively spared. The decrease in cortical NA, as assessed by DBH immunohistochemistry, was approximately 60-70% of normal levels in those animals showing a substantial P300 attenuation [7].

Preliminary studies involving lesions of the LC nucleus in two monkeys suggest that BAEP peak latencies but not amplitudes are affected. The BAEP and P300 data suggest that the integrity of the LC-NA and its ascending fibers is important in auditory information processing at various levels of the neuraxis. The fact that P300 amplitude but only BAEP latency is affected following lesions of the LC nucleus suggests that LC-NA function differs at various levels of stimulus processing. The P300 data, like the LC activation effects on EEG measures, are

very important because they provide evidence that LC activity is sufficient and/or necessary for the normal expression of electrophysiological events that are closely linked to crucial aspects of sensory processing and behavioral state. For this reason, these two lines of experimentation constitute a major part of our proposed studies.

PUBLICATIONS FROM YEARS 01-03

Full-length reports fully or partially supported by this grant and published or accepted for publication since the initiation of funding (04/01/87 - 08/01/89) are listed below:

1. Lewis, D.A., Campbell, M.J., Foote, S.L., Goldstein, M. and Morrison, J.H. The distribution of tyrosine hydroxylase-immunoreactive fibers in primate cortex is widespread but regionally specific. J. Neurosci. 7:279-290, 1987.

2. Pineda, J.A., Foote, S.L., and Nevile, H.J. Long-latency event-related potentials in squirrel monkeys: further characterization of waveform morphology, topography, and functional properties. Electroenceph. clin. Neurophysiol. 67:77-90, 1987.

3. Campbell, M.J., Lewis, D.A., Foote, S.L. and Morrison, J.H. The distribution of choline acetyltransferase-, serotonin-, dopamine-beta-hyroxylase-, and tyrosine hydroxylase-immuonreactive fibers in monkey primary auditory cortex. J. comp. Neurol. 261:209-220, 1987.

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5. Pineda, J.A., Foote, S.L., Neville, H.J., and Holmes, T.C. Endogenous event-related potentials in monkeys: the role of task relevance, stimulus probability, and behavioral response. Electroenceph. clin. Neurophysiol. 70:155-171, 1988.

6. Adams, L.M. and Foote, S.L. Effects of locally infused pharmacological agents on spontaneous and sensory-evoked activity of locus coeruleus neurons. Brain Res. Bull. 21:395-400, 1988.

7. Pineda, J.A., Foote, S.L., and Neville, H.J. Effects of locus coeruleus lesions on auditory, long-latency, event-related potentials in monkey. J. Neurosci. 9:81-93, 1989.

8. Pineda, J.A., Holmes, T.C., Swick, D., and Foote, S.L. Brainstem auditory evoked potentials in squirrel monkey (Saimiri sciureus). Electroenceph. clin. Neurophysiol. 73:532-543, 1989.

9. Pineda, J.A., Holmes, T.C., and Foote, S.L. Intensity-amplitude relationships in monkey event-related potentials: parallels to human augmenting-reducing responses. Electroenceph. clin. Neurophysiol., in press.

10. Foote, S.L., Berridge, C.W., Adams, L.M. and Pineda, J.A. Electrophysiological evidence for the involvement of the locus coeruleus in alerting, orienting, and attending. Prog. Brain Res., in press.